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May 5, 2003

CERTIFICATE OF MAILING
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May 5, 2003
Date

Steven L. Highlander

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: Serial Number 09/061,417 entitled "METHODS AND COMPOSITIONS FOR THERAPEUTIC INTERVENTION IN CARDIAC HYPERTHROPHY" by Eric N. Olson et al.
Our ref: MYOG:029US; Matter No. 10017631

Commissioner:

Transmitted herewith for filing are:

1. Brief on Appeal Brief (an original and two copies);

2. A check in the amount of $160.00 for the filing of Brief on Appeal); and

3. A return postcard to acknowledge receipt of these materials. Please date stamp and mail this postcard.

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Very truly yours,

Steven L. Highlander

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#24
5/12/03

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Eric N. OLSON

Serial No.: 09/061,417

Filed: April 16, 1998

For: METHODS AND COMPOSITIONS FOR THERAPEUTIC INTERVENTION IN CARDIAC HYPERTROPHY

Group Art Unit: 1632

Examiner: M. Davis

Atty. Dkt. No.: MYOG:029US/SLH

BRIEF ON APPEAL

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May 5, 2003
Date

Steven L. Highlander

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APPEAL BRIEF

BOX AF
Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Appellant hereby submits an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the Office Action dated October 23, 2002. This brief is due on May 4, 2003, but since May 4, 2003 falls on a Sunday the due day is May 5, 2003, by virtue of the Notice of Appeal filed on February 24, 2003 and the return postcard stamped March 4, 2003. The fee for filing this Appeal Brief is attached hereto. Should any other fees be due, or the attached fee be deficient or absent, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account No. 50-1212/MYOG:029US/SLH. Please date stamp and return the enclosed postcard to evidence receipt of this document.

I. REAL PARTY IN INTEREST

The real party in interest is the assignee, Board of Regents, University of Texas, and the licensee, Myogen, Inc., Westminster, CO.

II. RELATED APPEALS AND INTERFERENCES

There are no interferences or appeals for related cases.

III. STATUS OF THE CLAIMS

Claims 1, 4, and 9 are pending in the application, claims 2, 3, 5-8, and 10-40 having been canceled. A copy of the appealed claims is attached as APPENDIX 1 to this brief.

IV. STATUS OF AMENDMENTS

No amendments have been submitted following the final office action.

V. SUMMARY OF THE INVENTION

The present invention involves a central mediator of cardiac hypertrophy and defines the molecular events linking calcium stimulation to cardiac hypertrophy. In particular, the present invention shows that Ca++ stimulation of the cardiac hypertrophic response is mediated through NF-AT3. Specification at page 4, lines 5-13. The invention provides methods of treating cardiac hypertrophy in a subject by inhibiting the function of NF-AT3 in a cardiomyocyte. Page 4, lines 5-10, 22-24. This method involves inhibiting the function of NF-AT3 and therefore relies on an interaction between an inhibitor and NF-AT3, thus the method also may comprise contacting the cardiomyocyte with an agent that binds to and inactivates NF-AT3. Page 4, lines 11-13, 19-20.

Furthermore, this agent may be a small molecule inhibitor or an antibody preparation. Page 4, lines 26-30; page 5, lines 1-2.

VI. ISSUES ON APPEAL

(i) Are claims 1, 4, and 9 enabled under 35 U.S.C. §112, first paragraph?

(ii) Is claim 1 inherently anticipated under 35 U.S.C. §102(b) by Haverich *et al.* ("Haverich"; Exhibit A), Reid *et al.* ("Reid"; Exhibit B), McCaffrey *et al.* ("McCaffrey"; Exhibit C) and Martinez-Martinez *et al.* ("Martinez"; Exhibit D)?

VII. GROUPING OF THE CLAIMS

The claims stand and fall together with respect to the rejections under 35 U.S.C. §112, first paragraph.

VIII. SUMMARY OF THE ARGUMENT

The rejection for lack of enablement draws specifically on MPEP §2164.03, requiring more detail from the specification to enable the claims. The examiner focuses heavily on his perceived unpredictability in the art, and relies almost exclusively on the adage that a patent not require undue experimentation from one of skill in that art, both of which appellant traverses as incorrectly applied to the facts of this case. Finally, the examiner advances a standard for enablement that runs counter to established case law. In sum, the rejection is flawed, both legally and factually, and should be reversed.

Appellant has addressed the enablement issue by supplying supporting experimental evidence through an expert affidavit (Exhibit E), as well as pointing out that, for the disputed

claims, the examiner has misapplied the undue experimentation standard. Reversal of the rejection is respectfully requested.

The prior art rejections are nothing more than an assemblage of references that discuss various unlinked elements of the claimed invention but never directly disclose the invention itself. No reference in and of itself contains the entire invention, and thus no reference actually anticipates the invention. Instead, the examiner relies on an inherency argument, where he has combined references that use cyclosporine (CsA) to combat transplantation disease with other references that show that CsA is also an NF-AT3 inhibitor. Still, the rejection improperly presumes that hypertrophy is associated with transplantation disease in order to find that these references truly anticipate the use of an NF-AT3 inhibitor in treating hypertrophy. However, the examiner fails to show where the nexus between treating transplantation disease and treating hypertrophy is proven. It is then further assumed by the examiner that any drug that treats transplantation disease will, by implication, treat hypertrophy as well. This assumption overlooks the fact that none of the clinical references even discuss hypertrophy. In sum, the rejection is based on a sketchy and poorly supported inherency argument which fails the legal standard for anticipation. Thus, this rejection too should be reversed.

IX. ARGUMENT

A. Rejection of Claims 1, 4, and 9 Under 35 U.S.C. §112, First Paragraph

The examiner has continued to allege that the specification fails to "enable" the claimed invention. The examiner's concern, primarily, is that due to the extreme unpredictability of a new art, it would constitute an "undue burden" for one of skill in the art to practice the claimed invention. The examiner focuses on MPEP § 2164.03, quoting that, "...the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention." The Examiner's argument, then, is that the specification does not contain enough guidance as to how to make or use a small molecule or antibody preparation to inhibit NF-AT3, that the specification and supporting documentation do not provide enablement for the concept of an agent directly binding to NF-AT3, and that the transgenic mice and in vitro data used to support the claims do not correlate to *in vivo* evidence of enablement. Appellants respectfully traverse this rejection and reiterate that the examiner has misapplied the relevant standard of undue experimentation.

Appellants acknowledge the Examiner's position that the use of NF-AT3 inhibitors to treat hypertrophy is not well-known. the information provided in the specification, however, coupled with what was known prior to this invention, would allow one of skill in the art to practice the invention. Furthermore, as seen in the Gorczynski Declaration (Exhibit E), there is clinical validity to the cellular and transgenic models relied up, which stands is start contrast to the examiner's assertion that the invention is not enabled. Dr. Gorczynski has reviewed and summarized the findings of Ritter *et al.* ("Calcineurin in Human Heart Hypertrophy,"

Circulation, 105:2265-2269, 2002; Exhibit F), where the authors endeavored to prove in a human clinical setting what was seen in the transgenic mouse models, namely that NF-AT phosphorylation was altered (*i.e.*, dephosphorylated and thereby more active) in hypertrophic hearts compared to normal heart tissue. Their findings that NF-AT2 was indeed dephosphorylated and more active in hypertrophic human hearts are strongly supportive of the inventors' paradigm, as well as of the transgenic models. In the words of Dr. Gorczynski, this work "validated the present inventors' notion of targeting NF-AT3." The examiner has failed to adequately address these statements.

Not only does the examiner appear to misapply MPEP §2164.03, he also appears to have ignored parts of that section that support Appellant's position. "The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required." MPEP §2164.03. Appellants have supplied working examples of NF-AT3 inhibitors preventing cardiac hypertrophy, but examiner has argued that the examples given in the specifcation (see pages 16, 24, 25, 28, 29, 30, 6, Examples 6 though 9) are insufficient and rely solely on transgenic models. In response, Appellants provided the Gorczynski's Declaration, which supports the use of these models as a reliable and accurate method for predicting clinical applicability. The examiner has provided no meaningful rebuttal of the facts as set forth in the Gorczynski Declaration.

Additionally, the examiner's criticism seems to rise to the level of requiring a working model, and according to MPEP §2164.02 "an applicant need not have actually reduced the invention to practice prior to filing." It is important to remember that "because only an enabling disclosure is required, applicant need not describe all actual embodiments. The absence of working examples will not by itself render the invention non-enabled. Furthermore, a single

working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled." MPEP §2164.02. Examples 6 through 9 clearly show *in vivo* proof that use of NF-AT3 inhibitors can be a method to treat hypertrophy, and while these examples take advantage of transgenic animals, they make comparisons to non-transgenic animals for their conclusions.

As stated above, the examiner maintained his position on the experimental data in the application by asserting that the transfected cells and transgenic mice are not representative of what would be found in human subjects and, thus, that the data are not enabling for use *in vivo* for patients. Appellants again refer to the Gorczynski Declaration, regarding the validity of the transfection model and transgenic mouse model. In particular, Dr. Gorczynski's review of Ritter *et al.* states that the results provided there show *in vivo* evidence from a human clinical setting, albeit indirect, that there is an altered NF-AT phosphorlyation state in hypertrophied myocardium, demonstrating correlation. It further validates the notion of targeting NF-ATs therapeutically to combat hypertrophy by interfering with the NF-AT transcriptional cascade. The examiner's only rebuttal is to argue that the entire pathway from activation to hypertrophy has not been fully elucidated. While arguably true, this does not explain why Dr. Gorczynski's position is unsupported.

The examiner has also maintained the enablement rejection by arguing that the concept of a direct interaction with NF-AT3 is not enabled. In response, the Appellants referred the examiner to the scientific publications Molkentin, "The Zinc Finger-containing Transcription Factors GATA-4, -5, and –6" (*J. Biol. Chem.* 275:50, 38949-38952, 2000; Exhibit G), and Olson *et al.* "Remodeling muscles with calcineurin," (*BioEssays* 22:510-519, 2000; Exhibit H). Based on the results set forth in these manuscripts, it is clear that a person of ordinary skill in the art

would recognize that NF-AT3 does indeed interact with GATA-4, and if the Appellants' purported role for NF-AT3 is accepted (and the examiner has provided no evidence to suggest it is not a valid model), then such an interaction could be manipulated and modulated by methods well known in the art.

Perhaps the best information on this point comes from the Molkentin mini-review, which summarizes the state of the art as of over a year ago. This article states "GATA-4 also physically interacts by way of the C-terminal zinc finger with nuclear factor of activated T-cells-c4 (NFAT)." (p. 38951; also see Molkentin, *Cell* 93, 215, 1998; Exhibit I; and Morin, *EMBO J.*, 19, 2046, 2000; Exhibit J). What this review article makes clear is that the current state of the field of cardiac hypertrophy studies accepts that GATA-4 does indeed interact with NF-AT3, it provides additional guidance regarding the interaction, and further validates the inventors' paradigm and approach. Dr. Gorczynski's Declaration also supports this belief. These articles, coupled with the conclusions of Dr. Gorczynski, lend credence and support to the concept of using an inhibitor that has a direct interaction with NF-AT3.

Appellants lastly submit that the examiner's rejection goes beyond any reasonable enablement requirement for §112. Appellants refer the board to *In re Robins*, 429 F.2d 452 (CCPA 1970), cited by the *Lilly* court, stating, "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." Furthermore, *Robins* holds that a "specification which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement ... unless there is reason to doubt the objective truth of the statements therein." The *Robins* court also noted that "Section 112 requires nothing more than objective enablement.

How such teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance."

The examiner has maintained rejections against the use of antibodies, DTC's, GATA4 mimetics, and virtually any other agent disclosed in the specification. In regards to antibodies, the examiner has stated that "it would be undue experimentation for one of skill in the art to make and use the claimed single antibodies specific for NF-AT3." This conclusion runs contrary to the holding in *In re Wands*, 858 F.2d at 737 (Fed. Cir. 1988), which states that so long as there is "considerable guidance" in the specification and "all of the methods to practice the invention [are] known" then "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." While more enablement may be required where the art is unpredictable, there is no *per se* rule for a working model. The invention must simply enable one of skill in the art to practice that invention, and there is nothing contained in the current application that goes beyond the capabilities of one of skill in the art (MPEP §2164.01 - "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.").

Also instructive is *U.S. v. Telectronics, Inc.* 857 F.2d 778 (Fed. Cir. 1992), that "a patent need not teach, and preferably omits, what is well known in the art ... the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art." This statement can be true for all claimed species in the application, the uses of which are prevelant in the literature and the teachings of which are legion. Contrary to the above cited standards, the examiner appears to require scientific certainty for enablement. The examiner's standard for enablement is thus improper, and the resulting rejection should be reversed.

Appellants assert that the discussion above shows that the rejected claims do in fact enable one of skill in the art to practice the invention. The rejections continuously rise to a level or standard not supported legally or by the MPEP. The examiner appears to want not just proof of concept, not just enablement for one of skill in the art, but an actual model and blueprint for practice of the invention, and this standard is inappropriate. Reversal of the rejection is therefore respectfully requested..

B. Inherency Rejection of Claim 1 Under 35 U.S.C. §102(b)

Claim 1 is allegedly rejected by the examiner under 35 U.S.C. §102(b) as inherently anticipated by Haverich, Reid, McCaffrey, or Martinez-Martinez. Haverich and Reid are said to teach the use of CsA in treatment of transplantation disease. McCaffrey and Martinez-Martinez are said to teach that CsA is an NF-AT3 inhibitor. The examiner asserts that these references, coupled with an assumed but unsupported assertion that transplantation disease leads to hypertrophy, "inherently lead" to the claimed method.

For literal anticipation of a claim, "a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *PPG Industries Inc. v. Guardian Industries Corp.*, 37 USPQ.2d 1618, 1624 (Fed. Cir. 1996). Appellants assert that every element in claim 1 is not found in any of the prior art references. Claim 1 teaches treatment of ***hypertrophy*** by inhibiting the function of NF-AT3 in a cardiomyocyte using a compound that inhibits the function of NF-AT3. The Haverich and Reid references teach the use of cyclosporin A (CsA) for treatment of transplantation disease; they do ***not*** teach, much less suggest treatment of hypertrophy or effects on cardiac structure. They are instead directed towards improving cardiac ***function*** in a post-transplant environment. Additionally, while the McCaffrey and Martinez-Martinez references ***do*** teach that CsA is an

NF-AT3 inhibitor, they do not teach the use of an NF-AT3 inhibiting compound to treat hypertrophy.

The examiner, realizing the defect set out above, resorts to inherency. To establish anticipation by inherency, "the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill....' 'Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" (*In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997)), The examiner has stated that "it is notoriously well known that transplanted heart soon develops ventricular hypertrophy." This statement bears no relation to the invention or the references cited, is not supported by any additional citations or references, and fails to "make clear that the missing descriptive matter is necessarily present" as required by *Schreiber*. "'In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.'" (*Ex parte Tanksley*, 37 USPQ2d 1382, 1385 (BPAI 1994)). The examiner has merely stated that a connection exists and is "notorious" without any support this statement, or even providing an affidavit as to his expertise in the field or personal knowledge, as permitted under 37 C.F.R. §1.104(d)(2) and MPEP §2144.03. Therefore, Appellants assert that the examiner appears to have broadly misapplied the inherency standards, which requires certainty as required by *Ex parte McQueen*, 123 USPQ 37 (Bd. App. 1958).

In sum, there is no evidence from the cited references that hypertrophy had been treated or even analyzed, and there would be no reason to jump from improved cardiac function to the

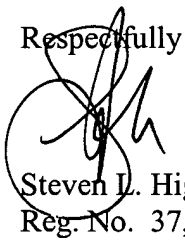
treatment of hypertrophy. The examiner supplied no references to link the concept of treating transplant disease and treating hypertrophy, and in an anticipation rejection, the reference(s) must teach the invention or literally or inherently anticipate the invention and that has not been shown. Because the references do not teach a treatment for hypertrophy, one of skill in the art would not be expected to infer from these references that CsA, and subsequently NF-AT3 inhibitors, were being used to treat hypertrophy. Because the rejection cannot be certain, it therefore fails to meet the standards required for an inherency rejection under 35 U.S.C. §102(b).

As each and every element of claim 1 is not found in the prior art, and as claim 1 is not inherently or literally anticipated, Appellants therefore respectfully request that the rejection under §102(b) be withdrawn.

X. CONCLUSION

It is respectfully submitted, in light of the above, that claims 1, 4, and 9 are sufficiently enabled to satisfy 35 U.S.C. §112, first paragraph, and that claim 1 is not anticipated under 35 U.S.C. §102(b), over the cited art. Therefore, appellants request that the Board overturn each of the pending grounds for rejection.

Respectfully submitted,



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Date: May 5, 2003

APPENDIX 1 -- PENDING CLAIMS

1. A method of treating hypertrophy in a subject comprising the step of inhibiting the function of NF-AT3 in a cardiomyocyte, wherein inhibition of NF-AT3 function inhibits hypertrophic gene expression, thereby treating hypertrophy.

4. The method of claim 1, wherein inhibiting the function of NF-AT3 comprises contacting said cardiomyocyte with an agent that binds to and inactivates NF-AT3.

9. The method of claim 4, wherein the agent that binds to and inactivates NF-AT3 is an antibody preparation or a small molecule inhibitor.

APPENDIX 2 -- EXHIBITS